

Regulatory Decisions to Include Genetics in Drug Product Labels: Moving Forward

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Overview

- The different sections of the product label – *What goes where*
- Learning from labels: Review label changes involving PGx information
- Compare and contrast different scenarios by which PGx information was added to labels
- Considerations for incorporating PGx into a development plan
- Lessons learned and future directions

Disclaimer

Past regulatory decisions related to adding genetics to drug labels are not necessarily precedents for future decisions

Science and regulatory policies are evolving rapidly and the future is unlikely to be identical to the past.



What Is The Purpose of a Label?

Vehicle for *communicating* the benefits and risks of using a medication

Basis for medical *decision-making* if the information is presented in a relevant, concise and comprehensive form

Component of *delivering* quality health care that leaves room for judgment and control in making decisions for individual patients



What Information Is In a Label?

Full Prescribing Information

HIGHLIGHTS

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

6 ADVERSE REACTIONS

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Pharmacogenetics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis,
Impairment of Fertility

13.2 Animal Toxicology and/or
Pharmacology

14 CLINICAL STUDIES

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

FDA's Regulatory Authority for Updating Labels

- ✓ **21 CFR 201.57**

“...if evidence is available to support the safety and effectiveness of the drug only in *selected subgroups*...the labeling shall describe the available evidence [and] identify specific tests needed for selection or monitoring of patients who need the drug...”

- ✓ **Title IX of FDA Amendments Act (FDAAA)**

Post-marketing requirements for generating data related to drug safety in general patient populations or patient subgroups

- ✓ **Labeling Guidance Documents (Jan 2006 – Mar 2009)**

www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

Labels and Label Updates in the Genomic Era: Translational Challenges

- Labels and label updates will only become more complex because of the novelty of information
- Clinical utility* of genetic information is central to label decisions; how evidence is generated and how much there is will dictate label language
- Labels are static; science behind labels is dynamic so label updates (preventing harm) will be common

* Term used to measure the impact of genetic information on the assessment of those who will benefit or those at risk [Zineh and Lesko, Personalized Medicine, July 2009, 6 (4), pp 359-361]

Scenario I: Preapproval Genetic Information in Labels

NEW DRUGS

Trastuzumab and HER2+ tumors	preapproval, prospective
Imatinib and Kit+ GIST	preapproval, prospective
Dasatinib and PH+ ALL	preapproval, prospective
Maraviroc and CCR5+ HIV-1	preapproval, prospective
Tetrabenazine and 2D6 (Based on DDI)	preapproval, retrospective
Erlotinib and EGFR+ tumors*	preapproval, retrospective
Nilotinib and UGT hyperbilirubinemia	preapproval, retrospective

* Tumor EGFR protein expression status removed from label in April 2009

- ➡ Linked co-development provides best opportunity to obtain evidence of clinical utility for both test and drug
- ➡ Strength of evidence comes from prospective hypothesis, RCT and replication
- ➡ Some examples of early phase studies providing evidence of clinical utility (safety) of test to predict side effects and optimize dosing
- ➡ Company assumes primary responsibility for generating evidence

Example: Co-Development of Tropism Test and Maraviroc

- HIV-1 co-receptor tropism assay was used in maraviroc clinical development program
- Approved label: Test clearly intended to select patients for treatment based on clinical outcomes
 - **Highlights** “Tropism testing is required for appropriate use...”
 - **Indications and Usage** “Tropism testing must be conducted with a *highly sensitive tropism assay*...”
 - **Microbiology** “Detection of CXCR4-using virus prior to initiation of therapy Is associated with reduced virologic response”
 - **Clinical Studies** “Clinical efficacy and safety derived from... subjects infected with CCR5-tropic HIV-1”
 - **Medication guide** “Your doctor will do a blood test to see if you’ve been infected with CCR5-tropic HIV-1 before prescribing SELZENTRY”

Source for Label: Selzentry (Nov 2009)

Example: Tetrabenazine (Xenazine) and CYP2D6 Poor Metabolizers (PMs)

- No studies conducted in CYP2D6 PMs; however, PMs anticipated to have higher (unsafe) exposure based on results of DDI study w/ paroxetine (CYP2D6 inhibitor)
- Approved label: Lower dose recommended for CYP2D6 PMs
 - **Clinical Pharmacology** “It is likely that the exposure to α -HTBZ and β -HTBZ would be increased compared to subjects who express the enzyme (EMs), with an increase similar to... strong CYP2D6 inhibitors (3- and 9-fold, respectively)
 - **Warnings** “Doses above 50 mg should not be given without CYP2D6 genotyping.”
 - **Laboratory Tests** “Before patients are given a daily dose greater than 50 mg, they should be tested for the CYP2D6 gene...”
 - **Dosage and Administration** “For CYP2D6 PMs: Dosing is similar to EMs... except the maximum recommended daily dose is 50 mg.”

Source for Label: Xenazine (Aug 2008)

Scenario II: Post-Approval Label Updates With Genetic Information

LABEL UPDATES *

Abacavir and HLAB*5701	post-approval, prospective
Clopidogrel and CYP2C19	post-approval, prospective
Irinotecan and UGT1A1*28	post-approval, retrospective
6-MP and TPMT	post-approval, retrospective
Panitumumab/Cetuximab and KRAS	post-approval, retrospective
Carbamazepine and HLA-B*1502	post-approval, retrospective
Warfarin and 2C9/VKORC1	post-approval, retrospective

** Others: capecitabine and DPD (3/2003), azathioprine and TPMT (7/2005) and atomoxetine and CYP2D6 (10/2006)*

- ➡ Lacks a co-development link between test and drug
- ➡ Evidence of clinical utility often comes from observational, case control or cohort studies (not RCT)
- ➡ Strength of evidence usually relies on retrospective analysis of genetic associations (with or without prospective hypothesis)
- ➡ Study data often not generated by company

Example: Abacavir Hypersensitivity and HLA-B*5701

- Label updated ~10 years post-approval; the first PGx label update based on strong evidence of clinical utility from a prospective RCT
- Approved label: Testing clearly recommended (but not required) to prevent patient harm
 - **Black Box** “Patients who carry the HLA-B*5701 allele are at high risk for hypersensitivity rxn... screening for the allele is recommended”
 - **Contraindications** “Never restart... following a hypersensitivity rxn, regardless of HLA-B*5701 status”
 - **Warnings and Precautions** Description of allele as a risk factor for hypersensitivity and results of PREDICT-1
 - **Medication guide** “Your risk of this allergic rxn is much higher if you have a gene variation called HLA-B*5701”

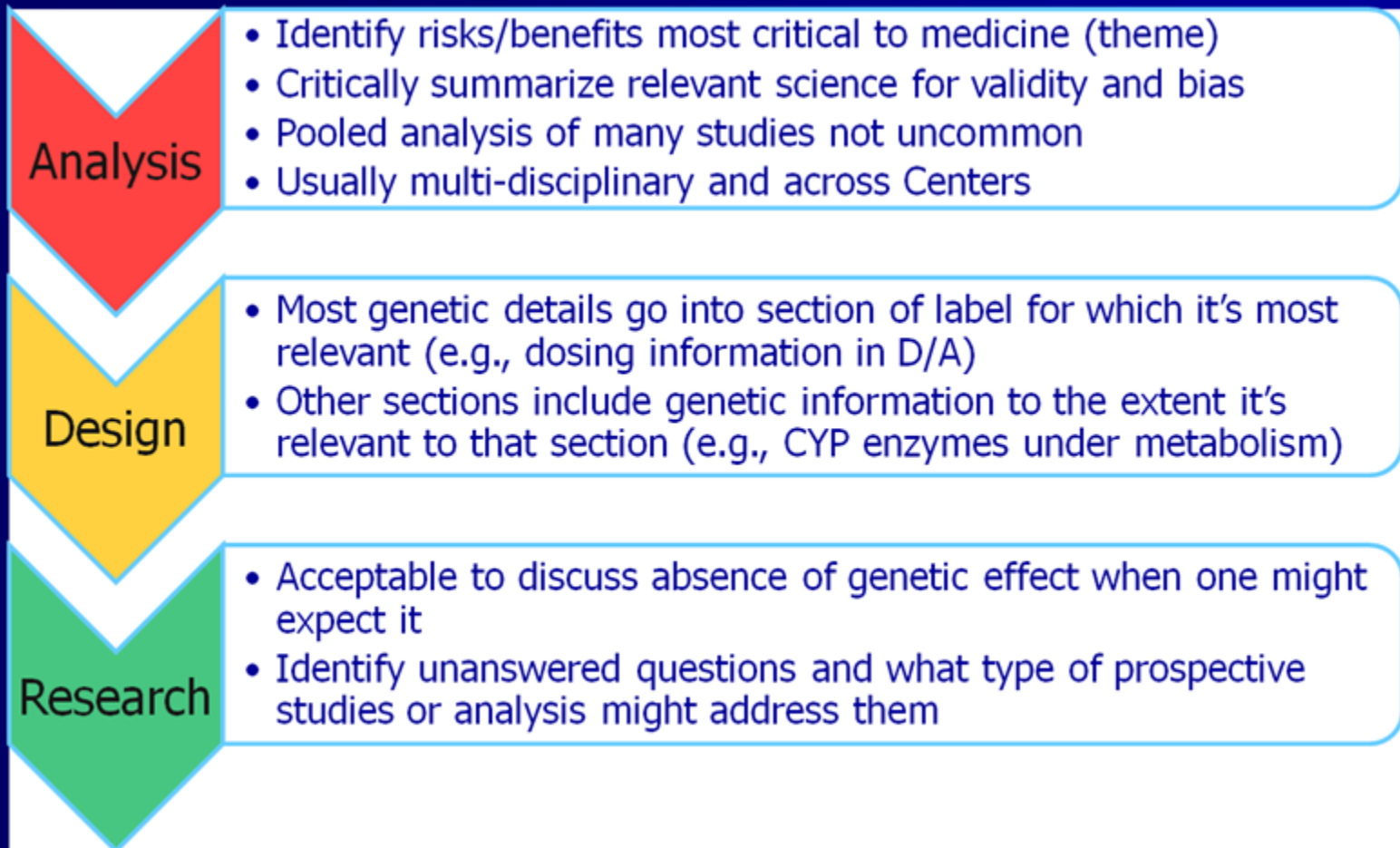
Source for Label: Ziagen (Dec 2008)

Example: Clopidogrel and CYP2C19 PMs

- Label update March 2010, based on new data from a prospective randomized study
- Label: Certain patients may not effectively convert clopidogrel to active form; tests are available to determine CYP2C19 status
 - **Black Box** “Effectiveness of Plavix depends on activation.... Poor metabolizers treated with Plavix at recommended doses exhibit higher CV event rates.... Tests are available to identify a patient’s CYP2C19 genotype”
 - **D & A** “An appropriate dose regimen for this patient population has not been established in clinical outcome trials”
 - **Pharmacogenomics** “The CYP2C19*1 allele corresponds to fully functioning metabolism, while CYP2C19*2 and *3 alleles are non-functional”

Source for Label: Plavix (Mar 2010)

General Step-Wise Process For Updating Labels: What to Say and Where to Say It



Updating Labels Is An Iterative Process

Ex: Warfarin (2007- 2010)

Warfarin CYP2C9 and VKORC1

August 2007 – Clinical pharmacology (PK, MOA, PD, metabolism, PGx); Precautions and D/A Sections

"The lower initiation doses should be considered for patients with certain genetic variations in CYP2C9 and VKORC1 enzymes"

January 2010 – Additional information added to D/A Section

"The patient's CYP2C9 and VKORC1 genotype information, when available, can assist in the selection of the starting dose. Table 5 describes the range of stable maintenance doses observed in multiple patients having different combinations of CYP2C9 and VKORC1 gene variants."

CYP2C9-VKORC1 Genotypes Used to Stratify Patients into Different Maintenance Dose Ranges

Table 5: Range of Expected Therapeutic Warfarin Doses Based on CYP2C9 and VKORC1 Genotypes[†]

VKORC1	CYP2C9					
	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3
GG	5-7 mg	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg
AG	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg
AA	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg

[†]Ranges are derived from multiple published clinical studies. Other clinical factors (e.g., age, race, body weight, sex, concomitant medications, and comorbidities) are generally accounted for along with genotype in the ranges expressed in the Table. VKORC1 -1639 G→A (rs9923231) variant is used in this table. Other co-inherited VKORC1 variants may also be important determinants of warfarin dose. Patients with CYP2C9 *1/*3, *2/*2, *2/*3 and *3/*3 may require more prolonged time (>2 to 4 weeks) to achieve maximum INR effect for a given dosage regimen.

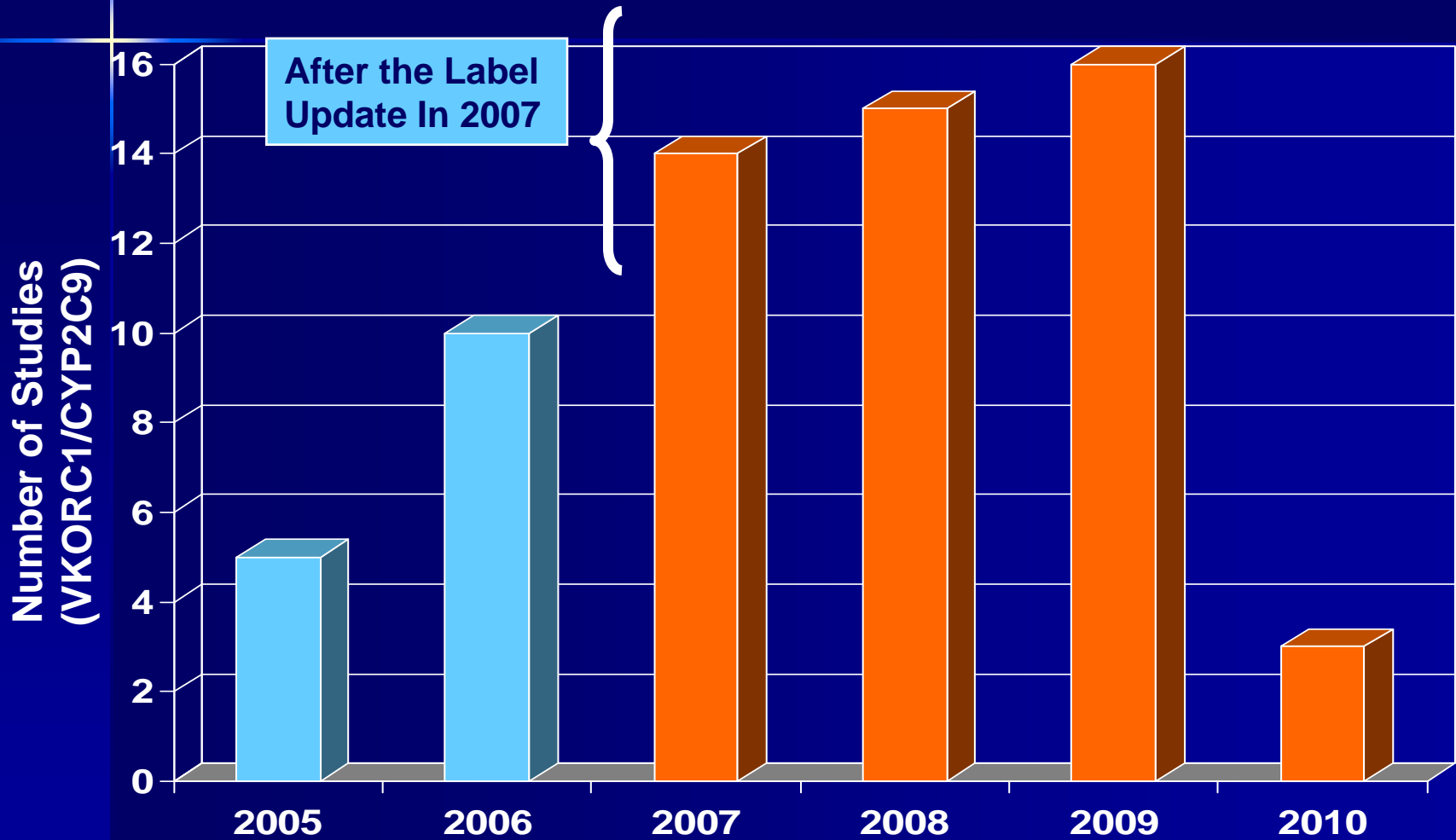
LOW 

MEDIUM 

HIGH 

Central Theorem of Label Updates: The clarity of genetic information in labels depends on how well genetic associations have been studied; insufficient clinical evidence about implications of gene sequence variations will lead to ambiguous or uninformative label updates

Published Studies Supporting the Use of PGx Testing for Warfarin



Professional Clinical Guidelines/ Professional Society Positions On PGx Testing for Warfarin

- **American Association for Clinical Chemistry:** *A national policy which promotes greater use of personalized medicine, particularly in regards to warfarin dosing levels, is warranted.*
- **College of American Pathologists:** *There is ample evidence of clinical validity and utility for pharmacogenomic testing for warfarin metabolism.*
- **American College of Chest Physicians Guidelines:** *“we suggest against pharmacogenetic-based dosing until randomized data indicate that it is beneficial.”*
- **American College of Medical Genetics:** *“...there is insufficient evidence at this time to recommend for or against routine CYP2C9 and VKORC1 testing in warfarin-naïve patients.” However, such testing “...may be useful and warranted in determining the cause of unusual therapeutic responses to warfarin therapy.”*
- **California Technology Assessment Forum:** *the use of CYP2C9 and VKORC1 genotyping did not meet its criteria for recommendation.*
- **Association for Molecular Pathology:** *Recommended additional research.*
- **American Society of Hematology:** *Recommended further clinical research. ASH does not support the use of pharmacogenomic testing to guide initial dosing or ongoing treatment of warfarin.*
- **Centers for Medicare & Medicaid Services:** *“the available evidence does not demonstrate that pharmacogenomic testing to predict warfarin responsiveness improves health outcomes in Medicare beneficiaries.
Pharmacogenomic testing to predict warfarin responsiveness is covered only when provided to Medicare beneficiaries who are candidates for anticoagulation therapy with warfarin and only then in the context of a prospective, randomized, controlled clinical study...”*

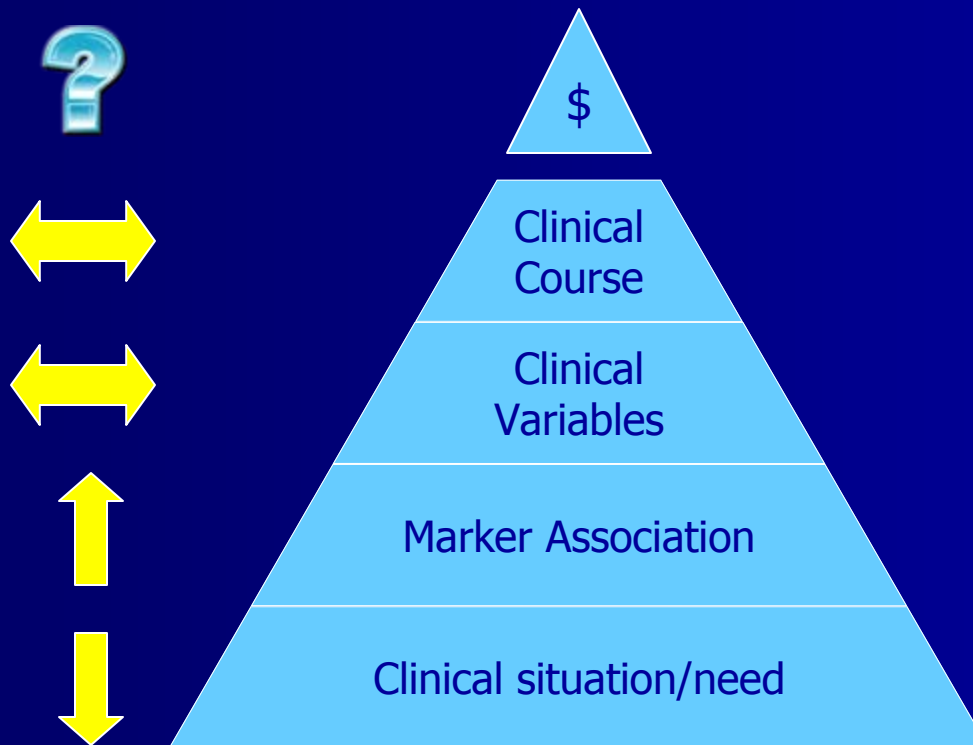
Comparison of Language Related to Tests and/or Testing: Review of Labels

	Available	Considered	Recommended	Required
Warfarin	N	Y	N	N
Clopidogrel	Y	N	N	N
Panitumumab	N	N	N	N
Cetuximab	N	N	N	N
Carbamazepine	N	N	Y	N
Abacavir	N	N	Y	N
Irinotecan	N	N	N	N
6-MP	Y	N	Y	N

- Prior clearance/approval of a genetic test, although preferred, is not a requirement for inclusion of test in drug label if risk/benefit is significantly improved
- Issues can arise when the intended use of an in vitro diagnostic is different than the intended use of the in vitro diagnostic in a drug label

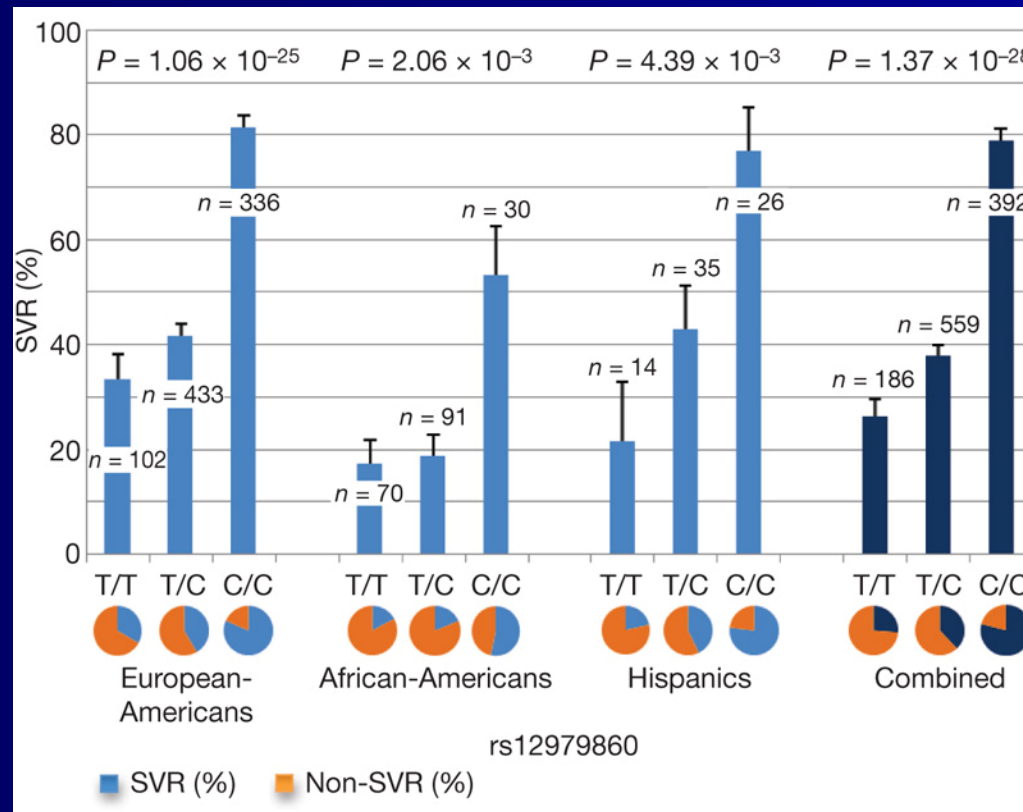
Pharmacogenetics Pyramid:

A Conceptual Framework for Evaluating the Value of a Genetic Test
Case #1: Efavirenz and CYP2B6 518G>T

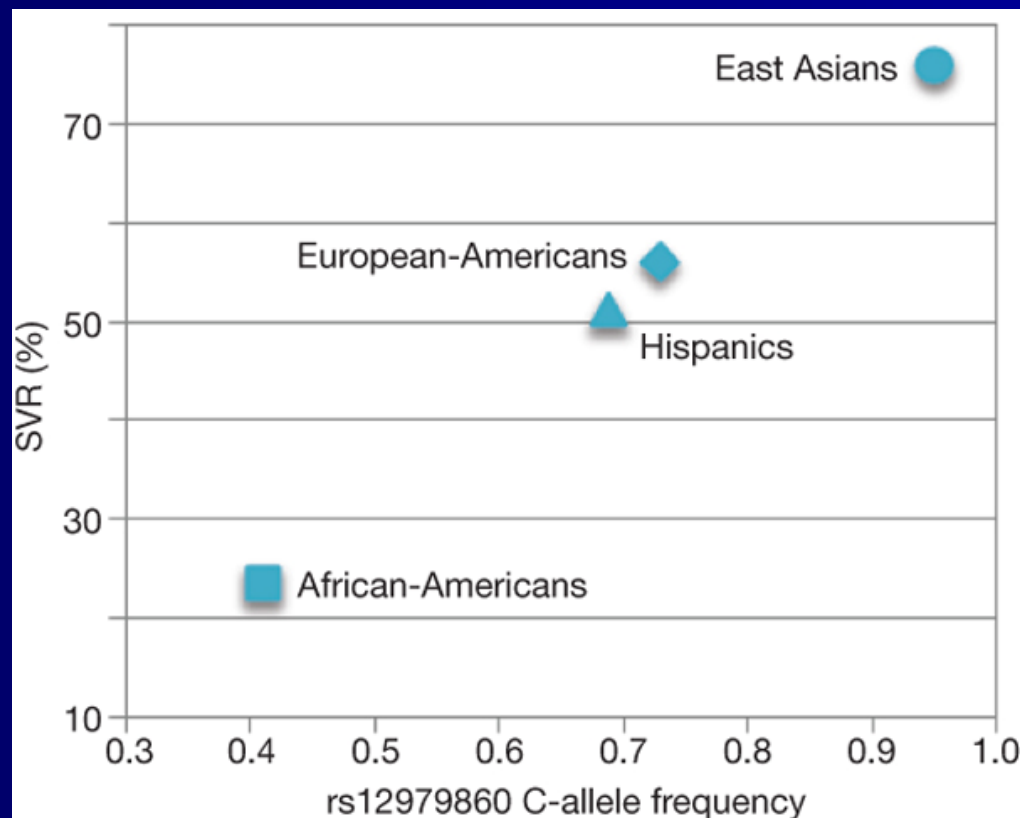


Adapted from Zineh and Lesko, Per Med 2009;6(4)

Sustained Virologic Response (SVR) to HCV treatment by *IL28B* (rs12979860) genotype

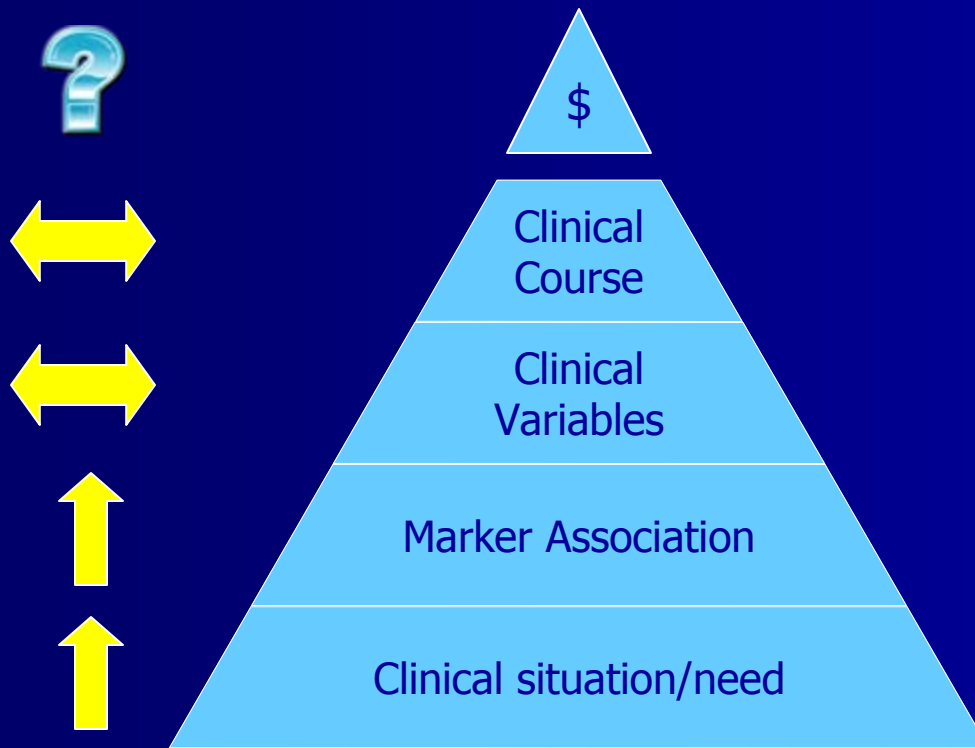


Rate of SVR and Allele Frequency Across Ethnic Groups

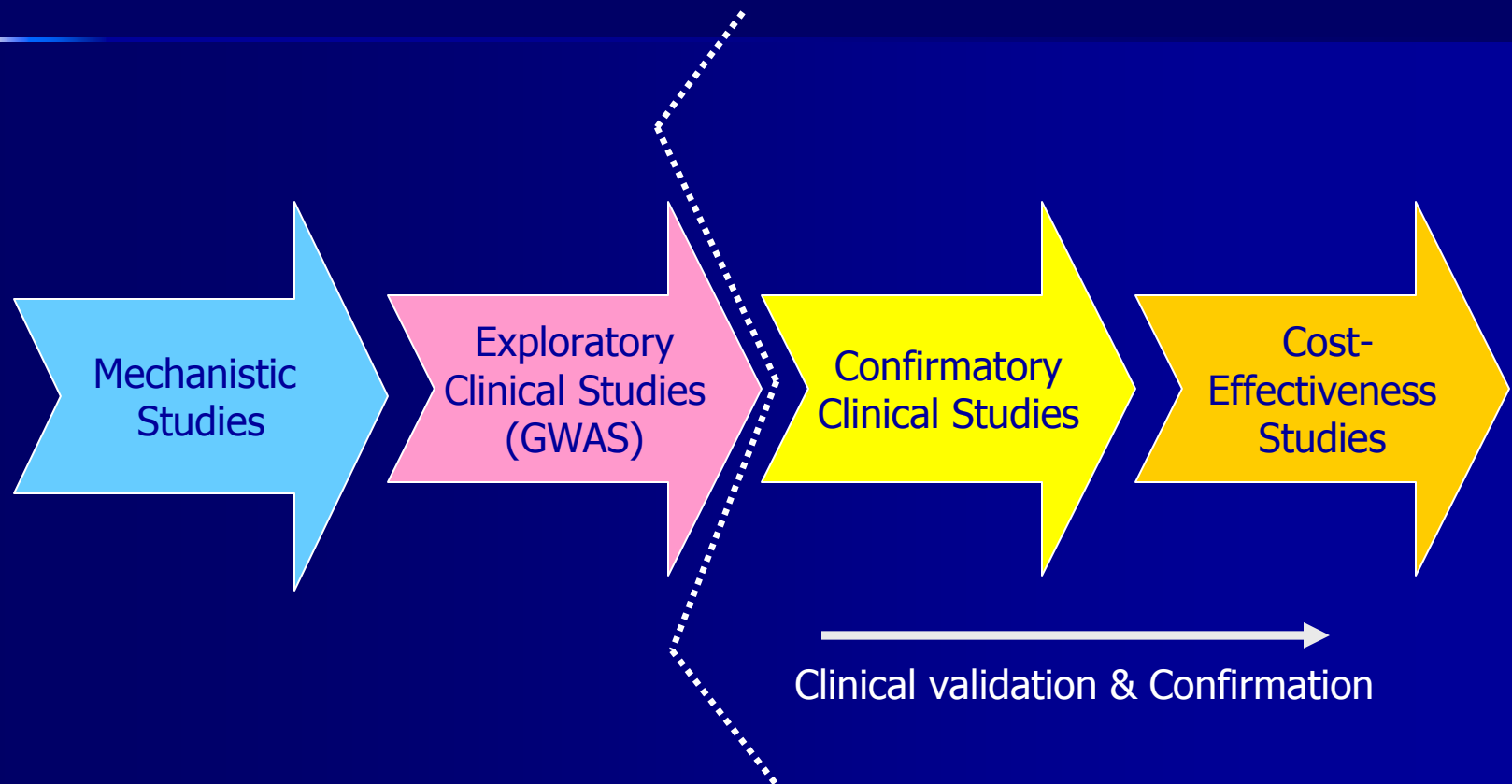


Ge D, Fellay J, Thompson AJ et al. Nature 2009;461:399

Case #2: HCV Treatment with Peg-IFN/RBV and *IL28B*



Implementation of PGx Testing



Adapted from Owen A. 17th CROI, Feb 16-29, 2010. San Francisco

Summary: Lessons Learned for Future Development of PGx Data Related to Labels

- **Lesson #1.** Evidence of clinical utility (risk/benefit) of in vitro diagnostic is paramount and central to inclusion of genetic information in drug labels
 - Need consensus on how to generate the evidence and how much is needed, especially in the post-approval scenario
 - Anticipate prescriber and patient wants and needs to assure that information generated through research is actionable
- **Lesson #2.** Communication of genetic information in labels is complex
 - Need to think about and focus on the link between the intentions of genetics in labels with potential impact on clinical practice

Summary: Lessons Learned for Future Development of PGx Data Related to Labels

- **Lesson #3.** Many of the questions and issues related to genetics in labels can be addressed
 - Needed clearer regulatory policies, processes and authority within, and between, Centers in FDA
- **Lesson #4.** Many of the uncertainties about genetics expressed by industry and others can be addressed through guidance for industry
 - Clinical PGx in early drug development,
 - Efficiencies in clinical trials (adaptive, enrichment)
 - Co-development of tests and drugs
 - In vitro diagnostic multivariate index assays

Conclusions

- There are many past examples to learn from with respect to incorporating PGx information into a product label and (hopefully) into clinical use
- In the area of HIV therapeutics, we have yet to successfully make the leap over the barrier into clinical validation and confirmation
- Greater collaboration is needed among regulatory agencies, drug manufacturers and academic researchers, to better integrate PGx knowledge into a clinical development plan

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